Review

Beyond Traditional Stimuli: Exploring Salt-Responsive Bottlebrush Polymers—Trends, Applications, and Perspectives

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ABSTRACT: Bottlebrush polymers represent an important class of high-density side-chain-grafted polymers traditionally with high molecular weights, in which one or more polymeric side chains are tethered to each repeating unit of a linear polymer backbone, such that these macromolecules look like "bottlebrushes". The arrangement of molecular brushes is determined by side chains located at a distance considerably smaller than their unperturbed dimensions, leading to substantial monomer congestion and entropically unfavorable extension of both the backbone and the side chains. Traditionally, the conformation and physical properties of polymers are influenced by external stimuli such as solvent, temperature, pH, and light. However, a unique stimulus, salt, has recently gained attention as a means to induce shape changes in these molecular brushes. While the stimulus has been less researched to date, we see that these systems, when stimulated with salts, have the potential to be used in various engineering applications. This potential stems from the unique properties and behaviors these systems show when exposed to different salts, which could lead to new solutions and improvements in engineering processes, thus serving as the primary motivation for this narrative, as we aim to explore and highlight the various ways these systems can be utilized and the benefits they could bring to the field of engineering. This Review aims to introduce the concept of stimuli-responsive bottlebrush polymers, explore the evolutionary trajectory, delve into current trends in salt-responsive bottlebrush polymers, and elucidate how these polymers are addressing a variety of engineering challenges.
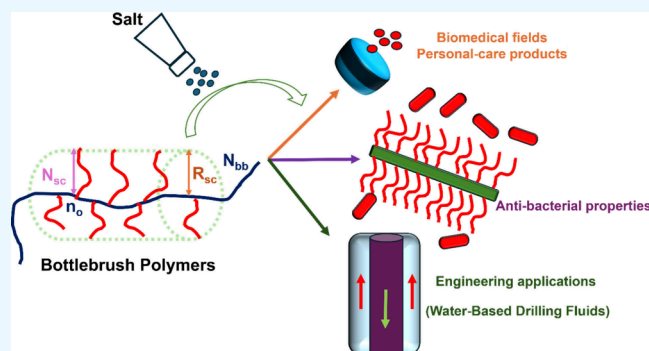
1. INTRODUCTION

Stimuli-responsive polymers are a remarkable class of materials that undergo significant alterations in their properties when subjected to changes in external conditions.[1−4] These polymers exhibit a wide range of compositions and architectures, including homopolymers,[5] statistical/block copolymers,[6,7] graft copolymers,[8] and molecular brushes.[9] A variety of external stimuli, including temperature,[10,11] pH,[12] ionic strength,[13,14] light,[15] electric fields,[16] and magnetic fields,[17,18] have been harnessed to tailor the properties of these polymers. This broad range of stimuli enables precise control over the polymer's behavior and functionality.

In response to these stimuli, these polymers typically undergo conformational changes, enabling them to adapt to different environmental conditions. Furthermore, they exhibit reversible solubility control,[19] allowing for adjustments in their solubility based on external factors. Another fascinating characteristic is their ability to undergo reversible self-assembly into polymeric micelles or vesicles, adding another dimension to their versatility.[20] The unique responsiveness of these polymers positions them as highly sought-after materials with applications across various fields. From drug delivery systems[21] to tissue engineering[22] and sensor/actuator systems,[23] the adaptability of stimuli-responsive polymers holds great

promise. Their capacity for stimuli-induced conformational changes and reversible self-assembly into micelles or vesicles opens up avenues for solutions in the design and development of advanced materials.[24] In addition to their widespread applications, ongoing research continues to explore new compositions, architectures, and stimuli-responsive behaviors, aiming to unlock even greater potential for these polymers in addressing complex challenges in science and technology. The dynamic nature of stimuli-responsive polymers makes them an exciting and evolving area of study with implications for numerous fields of research and practical applications.[24]
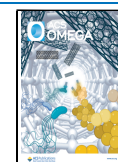
Over time, there have been several reviews focusing on bottlebrush polymers (BBPs) or stimuli-responsive polymers. Table S1 (Supporting Information) lists some recent examples of stimuli-responsive bottlebrushes, along with their synthetic routes, stimuli, and targeted applications However, a detailed
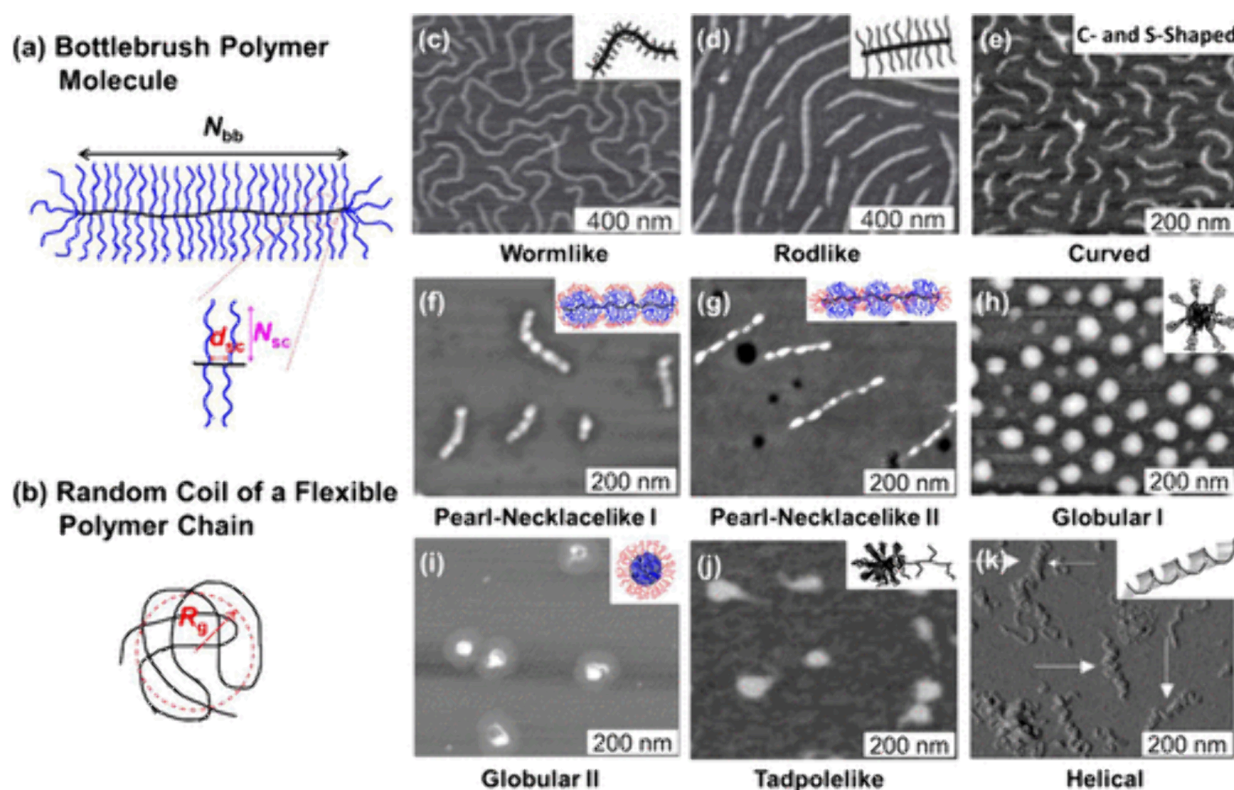
Figure 1. Schematics of a bottlebrush molecule with single-component homopolymer side chains (a) and a random coil of a linear flexible polymer chain (b). N_{bb}: degree of polymerization of the backbone. NSC: degree of polymerization of side chains. d_{sc}: distance between neighboring side chains. R_g: radius of gyration. (c–k) Various shapes of linear BBPs were observed experimentally: wormlike (c), rodlike (d), C- and S-shaped (e), pearl-necklace (f, g), globular (h,i), tadpole (j), and helical (k). Reproduced with permission from ref 32, copyright 2021 American Chemical Society.

review specifically on salt-responsive bottlebrush polymers is still lacking. This gap in the literature is what drives our motivation for this Review. A Review on salt-responsive bottlebrush polymers is essential due to the distinctive characteristics and promising applications of these materials. Bottlebrush polymers are unique in their structure, with densely attached polymeric side chains to a backbone, resulting in significant monomer congestion and unfavorable extensions of both the backbone and the side chains. The arrangement of these molecular brushes is intricately determined by the proximity of the side chains, which is considerably smaller than their unperturbed dimensions.[21]

Traditionally, the conformation and physical properties of polymers are influenced by external stimuli, such as solvent, temperature, pH, and light. However, the emergence of salt as a novel stimulus for inducing shape changes in these molecular brushes has garnered recent attention.[21–23]

It is well-established that smart polymeric materials can respond to external stimuli by adjusting their properties.[5,6] This responsiveness allows them to control functions such as ion and molecule transport and wettability and undergo conformational and chemical changes to adapt to their surrounding environment. These stimuli-responsive behaviors are relatively easy to achieve in solutions, where the Brownian motion of solvent molecules facilitates the displacement of macromolecular segments with low energy requirements.[20] Stimuli-responsive materials have been extensively studied for various advanced applications, including self-healing materials, self-cleaning surfaces, drug delivery systems, and bioengineering. Bottlebrush polymers make up a unique class of polymers

characterized by their distinctive morphological conformations. As previously discussed, BBPs can self-assemble into various architectures by simply adjusting their structural parameters. Consequently, any factor that alters the morphologies or properties of BBPs can serve as a regulatory parameter.[21–23]

Moreover, the energy required to induce changes in the assembled aggregates' external environment is significantly lower than that for covalently bonded species. BBPs can rapidly transform in response to various stimuli such as temperature, light, pH, and mechanical forces. This responsiveness enables them to adapt swiftly to changing environments.[25,26] Therefore, research has focused on investigating trigger-induced morphology transformations of single-molecule brushes in solution by varying the stimuli. The resulting changes in morphologies and properties have potential benefits for a wide range of applications, offering innovative solutions in diverse fields.

This Review aims to address several crucial aspects. First, it introduces the concept of stimuli-responsive bottlebrush polymers, highlighting their unique attributes and potential applications. Second, it explores the evolutionary trajectory of these materials, providing insights into the development of salt-responsive bottlebrush polymers over time. Lastly, it delves into current trends in the field, examining how these polymers effectively tackle a variety of engineering challenges. We believe that understanding the behavior and potential of salt-responsive bottlebrush polymers is pivotal for advancing materials science and engineering. By offering a comprehensive overview of the latest research in this area, this Review aims to provide valuable insights for researchers and engineers seeking
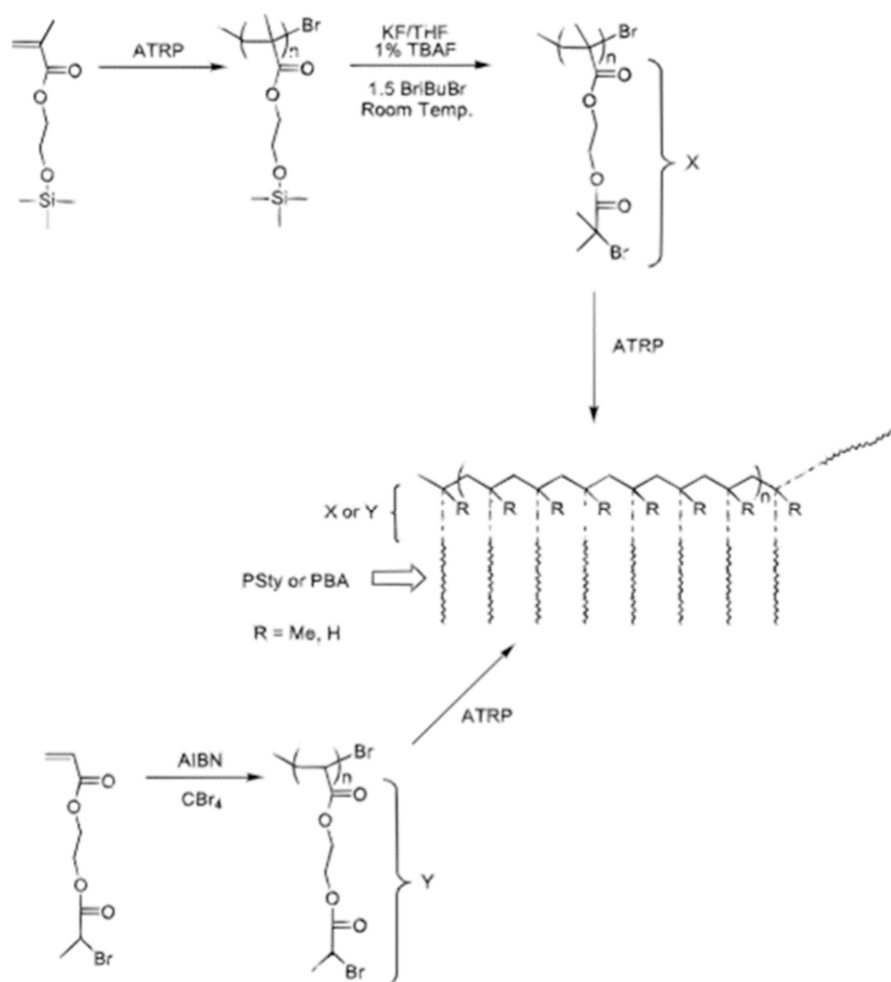
Figure 2. Two approaches were used to prepare the macroinitiators. In the first approach, conventional free radical homopolymerization of 2-(2-bromopropionyloxy)ethyl acrylate (BPEA) using AIBN in the presence of carbon tetrabromide yielded a macroinitiator with a molecular weight (M_n) of 27,300 g/mol and a broad molecular weight distribution (M_w/M_n = 2.3). This approach produced a polymer with a broad molecular weight distribution, leading to brush polymers with similarly broad distributions, regardless of the control over side chain polymerization. In the second approach, trimethylsilyl-protected 2-hydroxyethyl methacrylate (HEMA-TMS) was polymerized via ATRP and subsequently esterified with 2-bromoisobutyryl bromide (BriBuBr) using tetrabutylammonium fluoride (TBAF) as a catalyst. This method produced a well-defined macroinitiator, poly(2-(2-bromoisobutyryloxy)ethyl methacrylate) (pBIEM), with controlled molecular weight and low polydispersity. Reproduced with permission from ref 49, copyright 1998 American Chemical Society.

to design innovative materials with tailored properties for various applications.

2. NEED FOR TETHERING STIMULI RESPONSIVENESS TO BOTTLEBRUSH POLYMERS

Bottlebrush polymers (BBPs), commonly referred to as molecular brushes, constitute a distinctive subclass of graft copolymers wherein relatively short polymeric side chains are densely affixed through covalent bonds to a polymer backbone.[25−28] Researchers are focused on understanding these complex macromolecules, developing synthesis techniques, studying their molecular structures, examining their behavior in different environments, and exploring their practical applications.[29] The amalgamation of experimental, theoretical, and simulation studies has revealed several captivating traits and behaviors inherent to BBPs.[29] These include their molecular dimensions, anisotropic shapes, high density of functional groups, substantial and modifiable persistence length, stimuli-induced shape alterations, remarkably high backbone entanglement molecular weight, and

distinctive crystal habits—all stemming from the densely grafted nature of the brushes.[30−32]

BBPs have emerged with promising applications across diverse domains, spanning from the creation of photonic crystals,[33] surface coatings for lubrication,[34] and supersoft elastomers to drug delivery systems and the template synthesis of nanomaterials.[35,36] At the core of BBP molecular architecture lies a linear backbone featuring single-component homopolymer side chains, defined by three pivotal molecular parameters: the degree of polymerization (DP) of the backbone (N_{bb}), the DP of side chains (N_{sc}), and the average distance between two adjacent side chains (d_{sc}), or more commonly expressed, the grafting density of side chains (σ_{sc}) (Figure 1).

The high grafting density of side chains engenders steric repulsive interactions, propelling BBPs to adopt stretched conformations reminiscent of surface polymer brushes on solid substrates.[32] This conformational tendency results in bottle-brush polymers (BBPs) maintaining a stable cylindrical shape in suitable solvents despite both the backbone and side chains

being made of flexible polymers. This anisotropic molecular shape stands in contrast to the random coils and spherical shapes typically exhibited by linear, flexible polymer chains in similar solvent conditions.[32,37,38]

The tunability of the persistence length or Kuhn length within bottlebrush polymers stands out as a remarkable feature, providing a versatile tool for tailoring their structural characteristics.[39,40] This tunability is achieved through the manipulation of key parameters, namely the degree of polymerization of side chains (N_{sc}) and the grafting density of side chains (σ_{sc}), along with the careful selection of both backbone and side chain polymers.[40] In general, persistence length tends to increase with higher values of N_{sc} and σ_{sc}.[41,42] The experimental exploration of BBPs has yielded a diverse array of shapes, including wormlike, rodlike, C- and S-shaped, pearl-necklace, globular, tadpole, and helical conformations. Each of these shapes contributes to the rich and varied landscape of BBP structural motifs, showcasing their adaptability and potential for innovation in the realm of polymer science.[32]

As we already highlighted, the distinctive feature of BBPs lies in their high grafting density, where up to 4 chains per 1 nm of the backbone or even higher densities, resembling molecular "barbwires", can be achieved.[43] This density results in a highly congested and constrained molecular structure, which endows BBPs with unique properties. Notably, the steric repulsion between densely grafted side chains generates significant mechanical tension in the backbone. The ability to fine-tune this tension becomes feasible through the adjustment of parameters such as grafting density, solvent quality, and side chain length.[44] When these polymers are adsorbed onto a substrate, spontaneous scission of covalent bonds can occur, and tension amplifies from picoNewtons to nanoNewtons.[45,46]

Furthermore, in contrast to polymeric micelles formed by amphiphilic block copolymers, molecular brushes with amphiphilic block copolymer side chains exhibit the unique capability of forming stable unimolecular micelles with a cylindrical shape. This stability arises from the covalent attachment of side chains to the backbone,[43,47,48] adding another layer of versatility to the repertoire of BBP structures.

The inception of interest in molecular brushes can be traced back to the 1998 report detailing their preparation through atom transfer radical polymerization (ATRP) (Figure 2).[49] This groundbreaking method marked a turning point, introducing nanoscale objects characterized by precisely designed architecture and functionality.[43] These molecular brushes have since emerged as invaluable models in both biomedical and nanoengineering research, offering a platform for exploring intricate molecular interactions and paving the way for innovative applications. The ensuing years have witnessed burgeoning interest in the field of stimuli-responsive molecular brushes. This surge in research activity is evident through the escalating number of scientific papers dedicated to revealing the unique properties and utilities of these dynamic macromolecular structures. Researchers have been fervently delving into the intricacies of molecular brushes, seeking to uncover their full potential and exploit their distinctive characteristics for diverse applications.[50]

Recent efforts in molecular brush research have been particularly directed toward looking into stimuli-responsiveness into these structures. This strategic approach aims to harness and capitalize on the inherent dynamic properties of molecular brushes. The ability of these brushes to undergo

reversible conformational changes in response to external stimuli has become a focal point of exploration. Advanced techniques, such as atomic force microscopy (AFM), have played a pivotal role in this endeavor, enabling researchers to meticulously observe these dynamic changes at the single-molecule level.[50−53] This level of precision in characterization enhances our understanding of the nuanced behavior of molecular brushes and opens new avenues for their utilization in various scientific and technological domains.

The dynamic nature and the potential applications of stimuli-responsive molecular brushes hold their significance at the forefront of materials research and innovation. As researchers continue to uncover the intricate details of these macromolecules, the possibilities for their application in fields such as drug delivery, nanotechnology, and responsive materials are expanding.[53] Molecular brushes stand poised as a dynamic and versatile class of materials, continually contributing to the ever-evolving landscape of scientific discovery and technological advancement.

3. THE ART OF MAKING CONVENTIONAL BOTTLEBRUSH POLYMERS SMART

The rising need for "smart" materials, particularly in biomedical and engineering applications, has spurred an interest in synthetic polymers designed to exhibit environmentally responsive behavior.[32] Within the field of stimuli-responsive systems, a significant focus revolves around the investigation of straightforward homopolymers, which undergo reversible conformational changes in response to external stimuli such as temperature, pH, and light.[54] This phenomenon holds the promise of inducing noteworthy alterations in the physicochemical properties of both bulk materials and individual polymer molecules, as illustrated in Figure 3a. The exploration of stimuli-responsive polymers marks an important
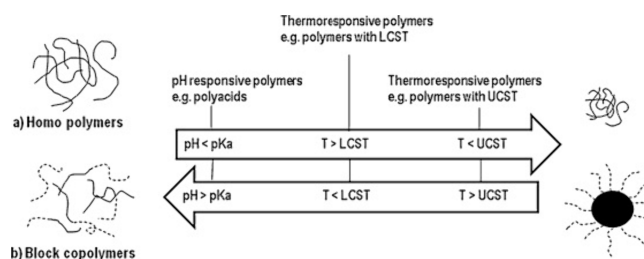

Figure 3. Conformational changes of polymeric-responsive systems in response to variations in pH and temperature are depicted in the context of both homopolymers and block copolymers. The schematic representation illustrates how these polymers undergo structural transformations based on environmental stimuli. In (a), the conformational changes of homopolymers are elucidated. The solid line indicates the responsive segment of the polymer, and the dotted line represents the hydrophilic region. As pH or temperature conditions change, the homopolymer exhibits alterations in its structure with the responsive block undergoing distinct conformational shifts. (b) extends this concept to block copolymers, where two different blocks with varying responsive behaviors are combined. The solid line represents the responsive block, which undergoes conformational changes in response to external stimuli, while the dotted line denotes the hydrophilic block, which remains relatively stable. The interplay between these blocks results in intricate conformational alterations of the entire polymer structure as pH or temperature conditions fluctuate. Reproduced with permission from ref 43, copyright 2010 Elsevier.

landmark in advancing the development of materials with tailored and dynamic functionalities. These polymers are designed to intelligently respond to changes in their external environment, providing a versatile toolkit for diverse applications in biotechnology, medicine, and engineering.[43]

In this context, homopolymers serve as fundamental building blocks for understanding the principles of stimuli responsiveness. By harnessing the inherent capacity of these polymers to undergo reversible conformational changes, researchers can fine-tune their properties based on specific external cues. The three primary stimuli—temperature, pH, and light—serve as key triggers for inducing these conformational changes, imparting a high degree of controllability and adaptability to the materials. As depicted in Figure 3a, the external stimuli initiate a cascade of molecular responses, leading to changes in the overall behavior and characteristics of the polymers. The ability to finely modulate the physicochemical properties of these materials offers a wealth of possibilities for tailoring their performance in response to specific application requirements.[43]

This research avenue is particularly crucial in the context of biomedical applications, where the demand for materials capable of responding to physiological conditions or external stimuli is paramount. The dynamic nature of stimuli-responsive polymers opens avenues for applications, such as controlled drug release, tissue engineering, and diagnostic tools. Moreover, in engineering applications, these materials present opportunities for developing responsive coatings, sensors, and actuators that can adapt to varying environmental conditions.[55−58] In essence, the exploration of homopolymers with stimuli-responsive behavior represents a cornerstone in the quest for "smart" materials. These materials not only showcase the elegance of molecular design but also pave the way for innovative solutions to address the evolving challenges in diverse scientific and technological domains.

In the same context, block copolymers are a fascinating range of polymers that exhibit stimuli-responsive behavior. For instance, Vancso developed molecular bottlebrushes featuring a redox-responsive poly(ferrocenylsilane) backbone and temperature-responsive poly(N-isopropylacrylamide) side chains.[55] These side chains were either evenly distributed or arranged in a gradient along the poly(ferrocenylsilane) main chain. The poly(N-isopropylacrylamide) chains were attached using azide−alkyne click chemistry or grafted from a PFS macroinitiator backbone using atom transfer radical polymerization, forming cylindrical-shaped molecular bottlebrushes. These bottlebrushes demonstrated both redox and temperature responsiveness (in water at temperatures above 32 °C, the bottlebrushes shrank to 70% of their original size due to the temperature-sensitive poly(N-isopropylacrylamide) side chains; upon cooling, they regained their original size, as confirmed by dynamic light scattering measurements), with each response being largely independent of the other. In another example, researchers developed amphiphilic thermoresponsive copolymer bottlebrushes using oligo(ethylene glycol)-containing macromonomers.[43] These bottlebrushes were prepared via a grafting-through method employing conventional free-radical and reversible addition−fragmentation chain transfer polymerizations. The copolymer bottlebrushes exhibited lower critical solution temperature behavior, which could be precisely adjusted over a wide range by varying the copolymer composition. In aqueous environments, these copolymer brushes formed flower-like micelles. These micelles

had a hydrophobic core made up of the polymer backbone and alkyl groups, while the poly(ethylene glycol) chains formed a hydrophilic outer layer.

Bottlebrushes synthesized through reversible addition−fragmentation chain transfer polymerization could form either single- or multiple-molecule micelles with uniform size distributions, depending on the length of the polymer chains. Removing one hydrophobic trithiocarbonate group resulted in increased hydrophilicity of the polymer, thereby lowering the cloud point, but did not change the aggregation numbers of the unimolecular micelles. The critical micelle concentration and drug loading capacity of the micelles were assessed using pyrene as a model hydrophobic drug. The synthesized bottlebrushes demonstrated a high loading capacity per gram of polymer. Interestingly, the loading capacity of these bottlebrushes was independent of the molecular weight of the copolymers and was solely determined by the number of hydrophobic units present.[56−58]

One advantage of bottlebrush block copolymers is their ability to self-assemble into much larger domains compared with linear block copolymers. This characteristic was first demonstrated by Li et al., who synthesized a series of high-molecular-weight bottlebrush block copolymers with polystyrene and poly(lactic acid) arms (Figure 4).[59] These copolymers
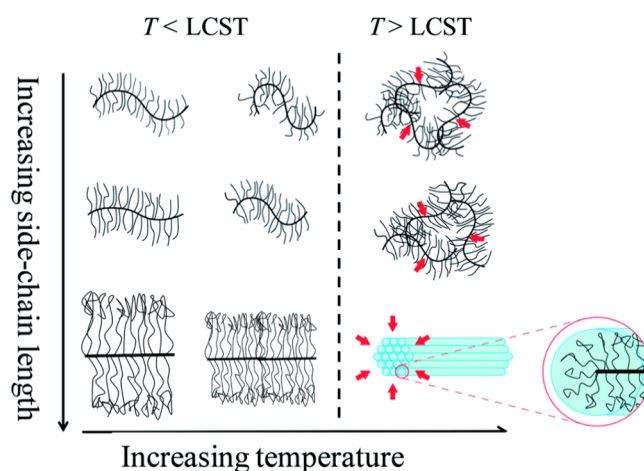

Figure 4. For bottlebrush polymers with short side chains, the side-chain length remains constant with temperature changes. Above the lower critical solution temperature (LCST), these polymers formed disordered aggregates. In contrast, for bottlebrush polymers with long side chains, the side-chain length decreases as the temperature increases. Above the LCST, these polymers exhibit lyotropic liquid crystal ordering due to the formation of structured aggregates. Reproduced with permission from ref 59, copyright 2014 Royal Society of Chemistry.

formed cylindrical domains ranging from 100 to 200 nm in size.[59] Further studies by the same group on brush-linear diblock copolymers revealed similar self-assembly behavior. Using scanning electron microscopy and UV−vis absorbance analysis, they observed the formation of block copolymer domains between 100 and 300 nm. These domains exhibited various morphologies, such as lamellar, cylindrical, or spherical, depending on the relative lengths of the polymer blocks.[59] Later, Bowden and colleagues expanded on this work by synthesizing and self-assembling high-molecular-weight di-, tri-, and tetrablock bottlebrush copolymers. They also explored bottlebrush block copolymers with different side chains and

backbones. Their research confirmed that bottlebrush block copolymers could form large domains and similar phase structures (cylindrical, lamellar, spherical) as linear block copolymers.[57] Moreover, they discovered that the morphology and domain size of these copolymers could be adjusted by altering the side chain and backbone lengths. Specifically, changing the side-chain length could tune the phase morphology, while the domain size was strongly influenced by the backbone length. This tunability offers significant flexibility in designing materials with specific structural characteristics for various applications.[57,59]

Thus, we observe that the research on bottlebrush copolymers has shed light on their fundamental self-assembly properties in both films and melted states. These copolymers self-assemble through a process called microphase segregation, resulting in the formation of large domains, often up to several hundred nanometers in size.[43,57] This size is primarily influenced by the length of the backbone. One notable characteristic of bottlebrush block copolymers is their ability to maintain ordered phases at very high temperatures, which hypothesizes them to be good candidates for developing stimuli-responsive polymers. This stability is attributed to their extended backbone, which keeps the polymer blocks separated effectively. Studies have demonstrated that for symmetric bottlebrush block copolymers the size of the domains shows a linear dependence on the degree of polymerization of the backbone. In contrast, asymmetric bottlebrush copolymers can form different structures such as cylindrical or spherical phases.[57] Additionally, bottlebrush copolymers with random side chains exhibit self-assembly into lamellar structures. These lamellae are smaller, typically ranging from 10 to 20 nm, which is comparable to the radius of gyration (R_g) of the side chains, leveraging the unique self-assembly properties of bottlebrush copolymers to create precise and functional nanostructures.[57]

In the current landscape of polymer science, several strategies exist to transform conventional polymers into stimuli-responsive materials. One prominent approach involves the metamorphosis of water-soluble polymers, introducing stimuli-responsive properties that can be finely tuned for specific functionalities. Water-soluble polymers, characterized by their solubility dependence on temperature, play a pivotal role in the development of materials featuring a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST). These polymers have found diverse applications across fields such as cell patterning, smart drug release, and DNA sequencing, showcasing their versatility in addressing a spectrum of biomedical and technological challenges.[59−62]

A noteworthy example of stimuli-responsive polymers is observed in thermoresponsive linear polymers, with poly(*N*-isopropylacrylamide) (PNIPAAm) serving as a representative illustration. PNIPAAm demonstrates a distinct phase transition around 32 °C. Below this critical temperature, the polymer and solution exist in a miscible state, whereas above it phase separation occurs. This transition is attributed to the release of water molecules associated with the isopropyl moieties in the side chains, leading to a controlled and reversible change in the material's properties.[59] Moreover, the behavior of bottlebrush polymers undergoes distinctive changes, depending on the length of their side chains, leading to intriguing temperature-dependent phenomena. When dealing with short side chains, the lengths of these side chains remain constant irrespective of temperature variations. However, the situation alters signifi-

cantly when the side chains are of considerable length (Figure 4). In the case of bottlebrush polymers with short side chains, a crucial temperature-related parameter is the LCST. Above this critical temperature, these polymers tend to form disordered aggregates. The term "disordered aggregates" implies that the molecular arrangement lacks a defined structure or order, and the components of the polymer assemble in a relatively chaotic manner. This behavior is characteristic of bottlebrush polymers with short side chains, and the transition above the LCST marks a distinct change in their structural organization. Conversely, when dealing with bottlebrush polymers possessing long side chains, a fascinating phenomenon unfolds. In this scenario, the length of the side chains exhibits a decrease with increasing temperature, particularly above the LCST. As a consequence of this temperature-induced modification in side-chain length, bottlebrush polymers with long side chains demonstrate the emergence of lyotropic liquid crystal ordering, (Figure 4).

Thus, the interplay between temperature and side-chain length in bottlebrush polymers leads to diverse and temperature-dependent structural outcomes. The distinction between disordered aggregates and lyotropic liquid crystal ordering provides valuable insights into the complex behavior of these polymers, paving the way for tailored applications and further exploration of their unique properties.[59]

Another class of stimuli-responsive polymers, the zwitterionic polymers such as poly(sulfobetaines), exhibit an upper critical solution temperature. These polymers demonstrate miscibility above a specific temperature, driven by the breakdown of interchain ionic cross-links. The ability to induce such controlled transitions in response to external stimuli positions these polymers as valuable tools in the design of responsive materials.[63−65] An intriguing illustration (Dr. Zhao's work) lies in the synthesis of a series of zwitterionic poly(sulfobetaine methacrylate)s (PSBMAs), where various N-substituents, such as *n*-alkyl, cyclohexyl, 2-hydroxyethyl, and phenyl, were systematically incorporated.[66] The objective was to unravel the effects of these N-substituents on the solution behavior of PSBMAs in water. This investigation brought to light a spectrum of behaviors exhibited by the PSBMAs, providing valuable insights into the interplay between different substituents and their impact on the polymer's response to changes in its environment. This systematic exploration of the impact of N-substituents on the solution behavior of PSBMAs provided valuable insights into the delicate balance between electrostatic and hydrophobic interactions. The findings have significant implications for the design of thermoresponsive zwitterionic PSBMAs with both UCST and LCST characteristics. Such tunable properties open up a myriad of opportunities for applications, including the development of thermoresponsive zwitterionic polymer brushes and nanogels. These materials hold promise in fields such as bioseparation and drug delivery, offering tailored solutions for specific biomedical and technological challenges.[66]

Crucially, we understand that the temperature of the phase transition in these polymers can be meticulously controlled by manipulating various structural parameters. Molecular weight, chain end groups, and overall structural configuration play pivotal roles in determining stimuli-responsive behavior. For instance, an increase in molecular weight typically leads to a decrease in the LCST due to polymer−solvent interactions. Additionally, the introduction of hydrophobic groups allows for the alteration of the hydrophilic−hydrophobic balance,

further enhancing the tunability of these materials. The strategic transformation of conventional water-soluble polymers into stimuli-responsive variants opens up avenues for tailoring materials with precise temperature-dependent behaviors. These advancements contribute to the expanding toolkit of smart materials, offering solutions to a wide array of challenges in biomedical, engineering, and materials science domains.[67,68]

pH-responsive materials represent a fascinating realm of dynamic responsiveness, primarily regulated by ionizable polymers characterized by a pK_a falling within the range of 3 to 10. Among these polymers, poly(acrylic acid) (PAA) serves as a notable example, showcasing remarkable conformational changes contingent upon the ionization state of its acidic or basic groups in response to fluctuations in pH.[69-71] The pK_a of PAA, a pivotal parameter in this context, holds sway over the polymer's conformational behavior. When the pH of the solution is below the pK_a value, PAA adopts a compact and collapsed form. However, as the pH escalates beyond pK_a, a dramatic transition occurs, causing the polymer to shift into a fully stretched conformation. This transformation is a result of electrostatic repulsion between the polymer segments, triggered by the alteration in ionization states of the acidic or basic groups within the polymer structure.[72]

Recent studies have expanded into advanced realms, with fluorescent probes emerging as pivotal components in various bioresponsive applications spanning from drug delivery to genomics. Among the myriad fluorescent dyes employed in these applications, fluorescein stands out as one of the most commonly used (Table S1).[73] In biomedical contexts, fluorescein boasts several advantages, including nontoxicity, high water solubility, and pH responsivity. A breakthrough method is presented in this context, offering a straightforward approach to the synthesis of pH-sensitive fluorescent molecular bottlebrushes. This involves the copolymerization of fluorescein O-methacrylate (FMA), a monomer containing fluorescein, with n-butyl acrylate (BA) in the side chains of the bottlebrush macromolecule.[73] The strategic choice of BA as the comonomer is driven by its low glass transition temperature ($T_g \cong -50\ °C$) and the propensity of poly(n-butyl acrylate) to adsorb onto specific surfaces, facilitating imaging using AFM. Despite the minute incorporation of FMA (0.25 mol %) during copolymerization, the resultant bottlebrushes exhibit highly desirable fluorescent properties.[73]

A distinctive feature of these fluorescent bottlebrushes is their ability to toggle fluorescence on and off by adjusting the pH of the solution from basic to neutral. This pH-dependent modulation of fluorescence introduces a dynamic element, positioning bottlebrushes as promising tools for molecular probing. This can be elucidated with photographs of irradiated samples containing the bottlebrush copolymers (Figure 5). When the conditions are neutral, only 508 nm excitation light is visible, signifying the absence of emission. Contrastingly, under alkaline conditions, the solution exhibits pronounced fluorescence, accompanied by the observation of green emission light at 570 nm, aligning with the emission wavelength recorded earlier on the spectrofluorometer.[73]

Their potential applications extend to direct visualization of drug delivery capsules and serve as molecular basicity indicators, showcasing versatility in diverse bioresponsive scenarios. The incorporation of fluorescein into the molecular structure not only enhances functionality but also marks a
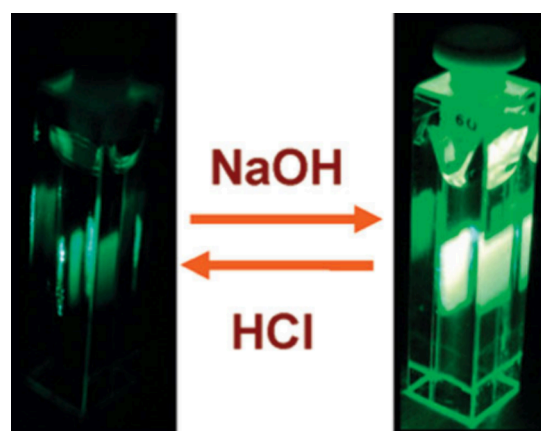

Figure 5. Solutions of bottlebrushes under neutral (left) and basic (right) conditions, Reproduced with permission from ref 73, copyright 2011 American Chemical Society.

significant advancement in the development of tailored molecular tools for bioimaging and therapeutic applications.

What is being imagined here is that pH-responsive polymers possess distinctive qualities because they can easily change shape when the pH levels are adjusted. This ability leads to interesting natural organization or separation on a very small scale, laying the groundwork for the creation of intelligent materials that can respond to their environment. The flexibility of pH-responsive polymers is especially beneficial in fields such as controlled drug delivery, where the release of drugs can be precisely controlled by changes in pH, ensuring more accurate therapeutic effects.

Though temperature and pH have been thoroughly investigated as external stimuli, light-responsive systems, despite their limited study due to the use of UV light, offer intriguing and attractive avenues of exploration. Linear polymers responsive to light typically incorporate photoresponsive units such as azobenzene, spiropyran, or diarylethenes. These units undergo reversible isomerization upon exposure to light irradiation.

A beautiful example can be cited by elucidating the work conducted by Henn and co-workers, who investigated the light-triggered unfolding of individual stimuli-responsive linear molecular bottlebrushes. These bottlebrushes are constructed from either homografted poly(methoxydi(ethylene glycol) acrylate-co-o-nitrobenzyl acrylate) (P(DEGMA-co-NBA)) or heterografted poly(ethylene oxide) (PEO) and poly(o-nitrobenzyl acrylate) (PNBA) side chains (Figure 6). The primary objective is to emulate the triggered unraveling observed in proteins like the von Willebrand factor and talin.[74] The article delves into the structural transformations of these molecular bottlebrushes, transitioning from compact globular to wormlike shapes under the influence of light stimuli.

The unique aspect of light responsiveness is its versatility, particularly when combined with thermal and pH sources, allowing the creation of dual-responsive systems with enhanced functionality and potential applications in various fields.

Since we are discussing how polymers respond to salt, it is crucial to understand how the thermoresponsive behaviors of graft and brush polymers depend on salt concentration. The addition of ions to an aqueous solution influences the position of the phase transition, a phenomenon known as the "Hofmeister effect".[75-77] This effect describes how different anions and cations can alter many properties of a solution.
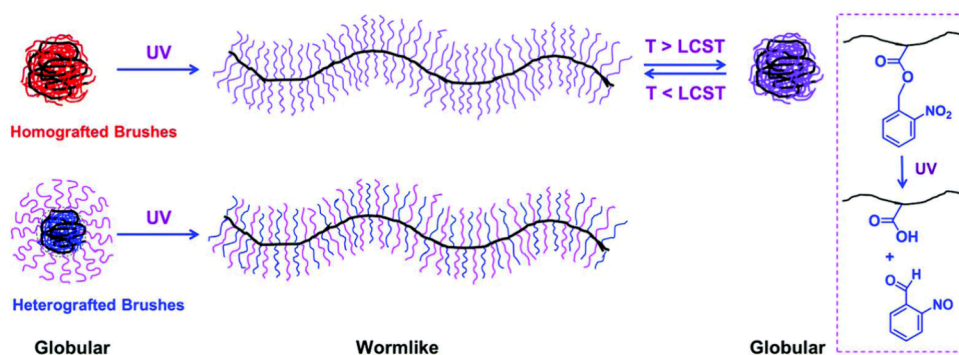
Figure 6. Stimuli-induced shape changing of single brush molecules from compact globular to wormlike conformations. Reproduced with permission from ref 74, copyright 2017 Royal Society of Chemistry.

Initially attributed to changes in water structure ordering, recent reports suggest the Hofmeister effect partly arises from direct interactions between ions and the solute.[75]

For poly(*N*-isopropylacrylamide), Zhang et al. identified three mechanisms contributing to the shift of the transition temperature (T_c):[78] (a) Dehydration of the amide groups by kosmotropic ions due to favorable hydration of the small ions, (b) changes in surface tension affecting the hydration of the hydrophobic parts of the polymer, and (c) direct interaction of the anions with the amide groups.

The first two mechanisms lead to the salting-out of the polymer (decrease in T_c), while the third leads to salting-in (increase in T_c). The overall behavior of an ion varies with its position in the Hofmeister series.[79] For example, chloride ions (Cl^-) show weak chaotropic properties and, despite weak binding to the amide group, generally cause a salting-out effect due to increased surface tension.[79]

It is indeed polymer brushes, consisting of polymer chains tethered to a substrate and stretching away from it in a "brush conformation", that are of significant interest. These brushes can react with external stimuli, often by reversible swelling and deswelling. PNIPAAm brushes have been observed to exhibit a broader transition compared to the polymer in solution, likely due to increased interactions between the closely tethered chains, which makes this interrelation so fascinating, especially when developing precise response polymers.[80]

Few studies have explored how additional salt affects the thermoresponsive behavior of grafted PNIPAAm chains. Jhon et al. investigated the influence of NaCl on PNIPAAm brushes with quartz crystal microbalance with dissipation monitoring.[81] They found a nonlinear shift of T_c to lower temperatures, unlike the linear decrease observed for PNIPAAm in solution. Ishida et al. used atomic force microscopy (AFM) and QCM-D to study PNIPAAm brushes with low grafting density in the presence of Na_2SO_4.[82] They observed unusual structural changes in the polymer layer with an increasing salt content. Naini et al. examined the effects of sodium halides on PNIPAAm brushes' switching kinetics and thermodynamics, noting that halides affected T_c according to the Hofmeister series.[83]

All these results essentially suggest that the Hofmeister effect and salt's impact on polymer behavior extends to bottlebrush polymers. The addition of counterions to SPB dispersions leads to the formation of local ordered structures among polyelectrolyte chains. This phenomenon has implications for the conformational changes observed in BBPs at varying salt concentrations. In concentrated SPB dispersions, counterions facilitate interactions among polyelectrolyte chains, affecting the overall conformation and responsiveness of the BBPs. Moderate strengths of counterions promote the formation of local ordered structures, which can either enhance or suppress the collapse of BBPs in response to salt, thus affecting their responsive behavior.[75]

Nevertheless, the major takeaway is that the influence of metal cations and counterions on the properties of salt-responsive bottlebrush polymers is essential for customizing their behavior for various applications. Understanding and manipulating the salt composition allows for precise control over the responsiveness of these polymers, thereby broadening their potential uses in different scientific and technological fields. In drug delivery systems, for instance, the responsive behavior of BBPs can be strategically employed to release therapeutic agents precisely at targeted sites within the body.[84−89] This targeted release improves treatment efficacy and minimizes side effects by ensuring that the drug is delivered exactly where it is needed. The ability of BBPs to respond to specific salt concentrations or types of ions can be used to trigger the release of drugs in response to the physiological environment of a specific tissue or organ.[75] Similarly, in the development of smart surfaces, the ability to modify polymer properties in response to external changes, such as variations in the salt concentration, can lead to the creation of materials with dynamic and tunable characteristics. For example, surfaces that change their wettability, adhesion, or other properties in response to environmental conditions can be designed. This can have significant implications for creating self-cleaning surfaces, responsive coatings, and adaptive materials that can adjust their properties for optimal performance in varying conditions.[90,91]

The manipulation of the salt-responsive behavior in BBPs can also extend to other applications. In environmental sensing and remediation, responsive polymers can detect and respond to pollutants or changes in environmental conditions, thereby providing real-time monitoring and adaptive responses. In biotechnology, responsive polymers can be used to create smart biomaterials that interact with biological systems in a controlled manner, enhancing the functionality of biomedical devices and implants.[75]

Thus, the ability to tailor the responsive behavior of BBPs by adjusting the type and concentration of metal cations and counterions provides a versatile tool for designing advanced materials with specific and dynamic properties. This approach not only enhances the performance and functionality of these materials in existing applications but also opens up new

possibilities for innovation across a wide range of scientific and technological domains. By understanding structure property relationships between ions and polymer chains, researchers and engineers can develop next-generation materials that meet the evolving demands of various industries and improve quality of life through advanced technological solutions, which in fact will be the focus of our next section.

4. EXPANDING THE REALM TO SALT-RESPONSIVE BOTTLEBRUSH POLYMERS

In recent decades, while thermal, pH, and light responsiveness have dominated discussions in the realm of bottlebrush polymers, a notable surge in research has emerged around a newly developed stimulus—salt. Salt-responsive bottlebrush polymers, also recognized as salt-responsive molecular brushes, present a distinct and promising avenue due to their unique behavior triggered by changes in the salt concentration. These polymers exhibit a remarkable ability to undergo tunable swelling and collapse, imparting versatility across a spectrum of applications. One key advantage lies in their capacity for controlled volume changes, particularly beneficial in drug delivery systems.[84] The reversible conformational changes in response to varying salt concentrations make these polymers valuable for the creation of smart coatings and surfaces, finding applications in antifouling coatings and responsive materials. For example, polyelectrolyte brushes undergo significant conformational changes, transitioning from fully extended chains in water to collapsed chains in salt solutions because of the electrostatic screening effect. This ion-responsive swelling-collapse transition depends on both the concentration and the type of ions present. This property offers a relatively straightforward method to tune surface friction, ranging from superior lubrication to ultrahigh friction, by simply adjusting the ionic environment.[92,93]

Their potential utilization in sensors and diagnostic devices is evident, leveraging the polymer's conformational shifts for salt-responsive sensing. In enhanced oil recovery processes, these polymers play a pivotal role in modifying the viscosity of injected fluids, thereby enhancing their efficiency in displacing oil from reservoirs.[75] Water purification technologies stand to benefit from the responsive nature of these polymers, allowing for the design of membranes or materials tailored for efficient water treatment. In the biomedical field, applications such as controlled drug release in physiological environments with varying salt concentrations align with the precision required in medical settings. Furthermore, the integration of salt-responsive bottlebrush polymers into nanomaterial synthesis opens avenues for developing responsive nanomaterials with applications spanning diverse industries.

As we already touched upon, among stimuli-responsive molecular brushes, salt-responsive molecular brushes have been much less explored. Müller and co-workers discovered that quaternized poly(2-dimethylaminoethyl methacrylate) brushes exhibited a conformational switch in response to varying concentrations of mono-, di-, and trivalent salts through electrostatic screening or to anionic surfactants through ionic complexation. This response illustrates the potential of salt-responsive brushes to undergo structural changes based on the ionic environment.[92]

Other studies on salt-responsive polymers, though not focusing on brush architectures, have primarily investigated ionic block copolymers due to their ability to form micelles.[93] These micelles can encapsulate and release substances in response to salt concentration changes. However, ionic block copolymers face challenges related to micellar instability, which is strongly influenced by their critical micelle concentrations (CMCs). The stability of micelles is crucial for maintaining their functional integrity, and fluctuations in salt concentration can lead to micelle disassembly or instability.[93] Salt-responsive polymers have found extensive applications beyond fundamental research, particularly in personal-care products such as wet tissues and hygiene diapers.[94] In these products, the polymers provide strength and integrity in a wet state with a higher ionic strength. The ionic charges of the polymers are screened by the salts, causing the polymer chains to become insoluble in water. This insolubility gives wet tissues and hygiene diapers the necessary structural strength to perform their function effectively.

Conversely, in environments with lower ionic strength, such as in deionized water or water with minimal salt content, these polymers become soluble due to the electrostatic repulsions between the ionic charges on the polymer chains. This solubility allows products to disintegrate and be flushed away, providing a practical solution for disposable personal care products. The dual functionality of salt-responsive polymers, with strength in saline environments and solubility in low-salt conditions, makes them highly useful for applications requiring temporary robustness and ease of disposal.

With this as the backdrop, it is evident how salt-responsive bottlebrush polymers could be promising materials to address the current challenges faced by the engineering field. These polymers have the potential to offer innovative solutions, particularly in a scientific manner that warrants further investigation. It is crucial to explore practical application areas where these polymers can be deployed effectively. By focusing on these specific areas (the subsequent section), we can better understand their capabilities and enhance their utility in various engineering applications.

5. HOW SALT-RESPONSIVE BOTTLEBRUSH POLYMERS ARE INFLUENCING THE REALM OF THE STIMULI-RESPONSIVE BOTTLEBRUSH

a. Early Development and Foundational Journey. In an earlier example of salt-responsive bottlebrush polymers, poly{[2-(methacryloyloxy)ethyl] trimethylammonium iodide} (PMETAI) cylindrical brushes have demonstrated intriguing behavior under varying salt concentrations.[92] The strong Coulombic repulsion among charged chains in the PMETAI brush leads to an elongated conformation. The introduction of salt to the solution acts as a screening mechanism, diminishing electrostatic interactions within the polyelectrolyte and resulting in a more collapsed conformation. Figure 7a illustrates the change in the hydrodynamic radii of the PMETAI brush in response to increasing NaBr concentration. A notable decrease in the apparent hydrodynamic radius (R_h) occurs upon the addition of salt, with a remarkable 8 nm decrease in R_h observed as NaBr concentration increases from 0 to 1 M. This distinct alteration in overall shape aligns with studies on planar and spherical polyelectrolyte brushes. Notably, at higher salt concentrations (beyond 1 M), the apparent R_h increases again, a phenomenon consistent with the findings in spherical polymer brushes. This behavior is attributed to specific interactions between bromide ions and cationic polyelectrolyte chains, leading to adsorption of bromine ions onto the chains and subsequent reswelling of the brushes. The collapse of the PMETAI brushes at a high salt
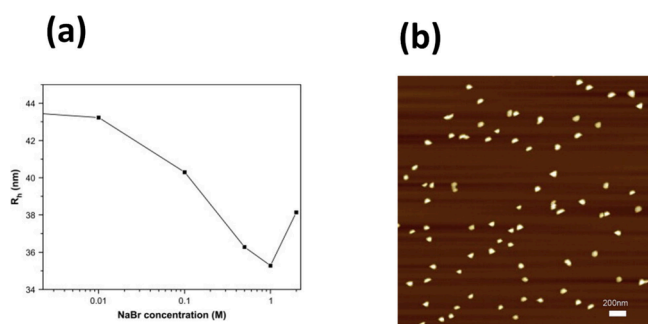
(a)

(b)

Figure 7. (a) Apparent hydrodynamic radii of the PMETAI brushes as a function of NaBr concentration. (b) AFM height image of PMETAI brushes on mica spin-coated from a 0.5 M NaBr solution. Z range is 12 nm. Reproduced with permission from ref 92, copyright 2008 Elsevier.

concentration is visually evident in AFM images, as shown in Figure 7b. The majority of brushes exhibit an ellipsoid-like conformation, with lengths less than 100 nm. The reasons for these observations, including the role of grafting density, are not entirely clear and may be linked to differences in the synthesis of brushes using PVP macromonomers. This detailed examination sheds light on the intricate response of salt-responsive bottlebrush polymers and their potential applications in diverse fields.[92] Table S2 (Supporting Information) summarizes the evolutionary snapshot of these responsive bottlebrush polymers.

With the evolving scientific realm, a distinctive class of cationic bottle-brush polymers had emerged, showcasing a unique ionic strength-dependent responsiveness.[94] The synthesis involves the creation of brush polymers, employing norbornene as the backbone and incorporating quaternary ammonium (QA)-containing polycaprolactone (PCL) copolymers as side chains. This intricate process, utilizing ring-opening metathesis polymerization (ROMP), ring-opening polymerization (ROP), and the click reaction, results in molecular brushes with noteworthy characteristics. In a low-ionic-strength aqueous environment, these brush polymers exhibit solubility driven by robust electrostatic repulsion among cationic QA groups.[94] However, the introduction of salt to augment the ionic strength initiates a remarkable transition in these brush polymers. The once-extended conformation undergoes a shift to a collapsed state, ultimately rendering the polymers insoluble in the solution. This transformation is attributed to the screening effect of salts, superseding the initially dominant electrostatic interactions among QA species and giving rise to hydrophobic–hydrophobic interactions.

Characterizing the salt-responsive property of PNPH-g-[PCL-co-P(CL-g-QA)] molecular brushes was undertaken through a meticulous exploration involving UV–vis spectroscopy and AFM. The molecular brushes were initially dissolved in deionized water at a concentration of 1 mg mL^{-1} (or 0.1 wt %). Subsequently, diverse copolymer solutions were created by introducing NaCl into these solutions. The visual inspection of the polymer brush solutions revealed intriguing transformations. The molecular brush with 20 mol % QA groups exhibited excellent solubility in salt-free water, resulting in a transparent aqueous solution. However, as the NaCl concentration increased, the solutions progressively turned turbid. In the ionic strength range of 0.15 to 0.3 M, the solution evolved from slightly unclear and turbid to milky

(Figure 8). Upon reaching an ionic strength of 0.4 M or higher, the solution transitioned into an opaque suspension with
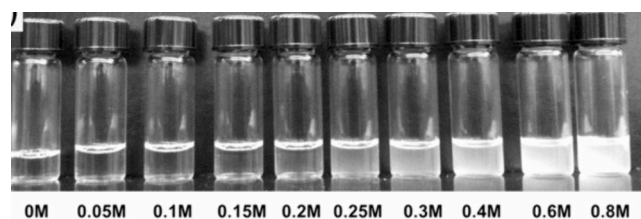

Figure 8. PNPH-g-[PCL-co-P(CL-g-QA)] (20 mol % QA) solutions in water (1 mg mL^{-1}) containing different ionic strengths of NaCl solution. Reproduced with permission from ref 94, copyright 2013 Wiley.

discernible precipitation at the vial's bottom. Notably, owing to its sufficiently high molecular weight, this molecular brush demonstrated the capability to produce robust films, holding significance for applications in personal-care products.[94]

In general, when polymers show improved solubility in a solvent upon the addition of salt, this suggests that the chain conformations are changing due to alterations in the solvent conditions. For instance, when salt is added to water, enhancing the solubility of polyzwitterions, it indicates that the chains may transition from a compact, globule-like state in salt-free aqueous solutions (a poor solvent-like condition) to a more expanded, coil-like state in salty solutions (a good solvent-like condition).[95]

However, the effects of added salt on the conformations of a polyzwitterionic chain cannot be solely explained by changes in the solvent quality. This is because water and salt ions can influence the net charge on a polyzwitterionic chain through protonation of zwitterionic monomers and adsorption of ions onto the monomers, respectively.[96] To control various properties of polyzwitterions in solutions, it is crucial to understand the relationship between charge regulation and chain conformations under both salt-free and salty conditions. Currently, the nature of polyzwitterionic chain conformations (whether globular, coil-like, or rodlike) and the effects of added salt on these conformations remain largely unknown. Analogies have been made by considering polyzwitterions as synthetic counterparts of intrinsically disordered proteins, and various hypotheses have been proposed regarding the conformations of these chains in dilute solutions. However, this leads to uncertainties not only in determining the overlap concentrations of polyzwitterions but also in understanding their complexation with polyelectrolytes, which is relevant in many biomedical applications.[95−97]

b. Amalgamating the Antipolyelectrolyte Effect and Salt-Responsive Bottlebrush Polymers. Post-2013, we see an interesting phenomenon being investigated in polymer brushes popularly called "the antipolyelectrolyte effect".[98−100] Intriguingly, certain zwitterionic polymer brushes defy the conventional behavior observed in polyelectrolyte brushes, exhibiting what is known as the "antipolyelectrolyte effect", a phenomenon in stark contrast to the "polyelectrolyte effect" displayed by typical polyelectrolytes. In the case of polyelectrolyte brushes, as depicted in Figure 9, these brushes assume a fully stretched chain conformation in pure water but transition to a collapsed chain conformation in a salt solution.[100] This transition occurs due to the introduction of salts, which effectively screen the electrostatic repulsions
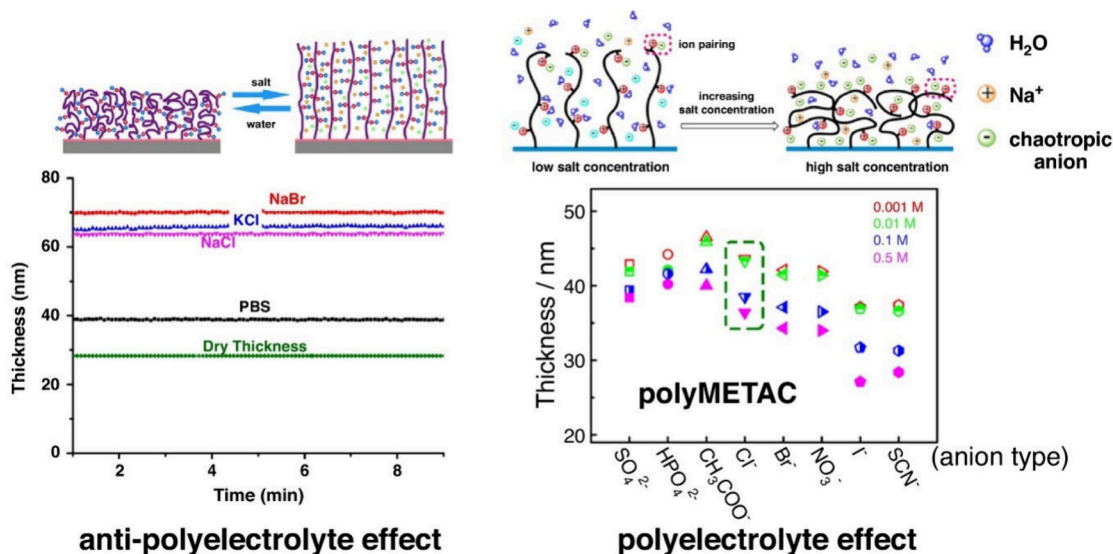
Figure 9. Schematic illustration for "polyelectrolyte effect" and "antipolyelectrolyte effect". Reproduced with permission from ref 103, copyright 2018 Elsevier.

between and within polyelectrolyte chains, resulting in the collapsed chain conformation and the exclusion of water from the brushes. The salt-responsive conformational change in polyelectrolyte brushes is a well-documented phenomenon observed in positively charged polyelectrolytes (e.g., poly [2-(methacryloyloxy)ethyl] trimethylammonium chloride (poly-METAC)) and negatively charged polyelectrolytes (e.g., polymethacryloyl ethylene phosphate), where electrostatic interactions with free ions significantly dictate their conformations.

In a remarkable departure from polyelectrolyte brushes, zwitterionic brushes exhibit a unique behavior—shrinking in water and stretching in salt solution. This property renders zwitterionic brushes more soluble in salt water than in pure water. The balanced presence of zwitterionic groups within the same chain and between neighboring chains governs their inter- and intrachain associations and interactions. Specifically, the addition of salts increases the screening effect, diminishing the attractive electrostatic interactions of ionic pairings between the zwitterionic groups. Consequently, this causes the polymer chain to stretch. Conversely, in pure water, without the presence of salts, the zwitterionic brushes exhibit a more collapsed conformation. This salt-responsive behavior of zwitterionic brushes, termed the "antipolyelectrolyte effect", stands in direct contrast to the behavior of polyelectrolyte brushes.[98−100] It is important to note that not all zwitterionic polymers exhibit a strong "antipolyelectrolyte effect", as the degree of this effect depends on the charge distributions and identities of the specific polymers. For example, conventional zwitterionic polymers like sulfobetaine methacrylate (SBMA)[101] and carboxybetaine methacrylate (CBMA)[102] show no significant change in dimensions with added salt, indicating a weak antipolyelectrolyte effect. On the other hand, polymers like polyVBIPS[103] exhibit a robust antipolyelectrolyte effect, stretching out their conformation in salt solutions.

Circumscribing on this discussion, the evolution of these salt-responsive bottlebrushes expanded in the past decade as we see in the pursuit of novel smart surfaces with applications in protein capture/release and surface friction/lubrication; zwitterionic, ionic-responsive polyVBIPS (poly(3-(1-(4-vinyl-

benzyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate)) brushes were successfully synthesized and characterized using the SI-ATRP method. These polyVBIPS brushes demonstrated a distinctive "antipolyelectrolyte effect", showcasing salt-responsive behaviors that allowed for a transition between states in water and salt solutions (Figure 9).[103] PolyVBIPS brushes exhibited a reversible surface wettability switch between water and saturated NaCl solutions. Salt solutions induced lower contact angles on polyVBIPS brushes compared with water solutions, indicating heightened surface hydration in salt environments. Remarkably, by manipulating salt concentrations and counterion types, polyVBIPS brushes displayed tunable behavior, transitioning from ultrahigh friction ($\mu \sim 100$) to moderate lubrication ($\mu \sim 10^{-2}$) and further to superior lubrication ($\mu \sim 10^{-3}$). Additionally, these polymer brushes exhibited salt-induced surface resistance to nonspecific protein adsorption from undiluted human blood serum and plasma at an ultralow fouling level (<0.3 ng/cm^2) (Figure 9).[103] The salt-responsive surface switching behaviors, encompassing transitions between surface friction and lubrication as well as protein adsorption and resistance, were attributed to cooperative effects arising from enhanced surface hydration and electrostatic screening. This pioneering work introduces a new class of zwitterionic, ionic-responsive polymer brushes, paving the way for their utilization as intelligent surfaces in dynamic applications.

c. Effect of Metal Cations and Counterions on the Properties of Salt-Responsive Bottlebrush Polymers. From the discussion, it becomes evident that metal cations and counterions significantly influence the properties of salt-responsive bottlebrush polymers. To gain deeper insights, we refer to the works of Xiao et al., who extensively studied the structural dependence of salt-responsive polyzwitterionic brushes with an antipolyelectrolyte effect.[98] The group attempted to investigate the effect of different anions (SO$_4^{2-}$, Cl, NO$_3^-$, or Br$^-$) and cations (K$^+$, Na$^+$, Mg^{2+}, or Ca^{2+}) on the surface hydration of the polyVBIPS, polySVBP, and poly-DVBAPS brushes. In their experiments, all salt concentrations of the different counterions were fixed at 1.0 M. The results indicated that polyVBIPS brushes consistently exhibited higher

contact angles compared to polySVBP and polyDVBAPS brushes in salt solutions with different anions. Specifically, brushes in SO_4^{2-} salt solutions had higher contact angles than those in Cl^-, NO_3^-, and Br^- salt solutions, following the hydration capability order of the Hofmeister effect (SO_4^{2-} > Cl^- > Br^- > NO_3^-) (Figure 10).[77]
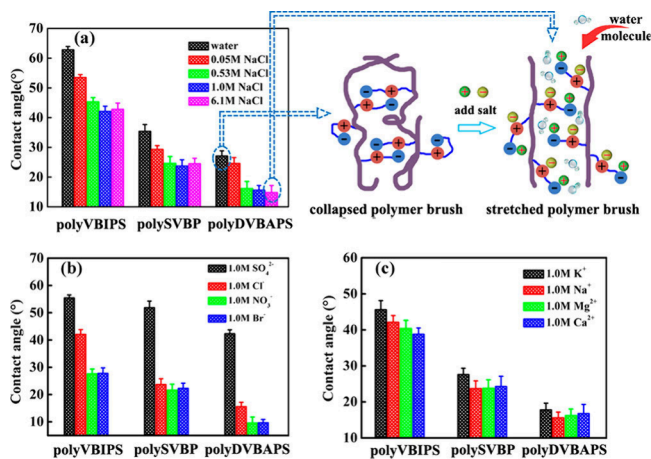

Figure 10. Contact angles of (a) NaCl solutions with different concentrations (0−6.1 M) (right, schematic of changes of the polymer chain conformation before and after salt addition) and (b,c) different salt solutions (1.0 M) containing (b) SO_4^{2-}, Cl^-, NO_3^-, or Br^- and (c) K^+, Na^+, Mg^{2+}, or Ca^{2+} on three polyzwitterionic brushes. Reproduced with permission from ref 98, copyright 2018 American Chemical Society.

Regarding cation effects, the contact angles of the polymer brushes in solutions containing different cations showed that the surface wettabilities of these zwitterionic brushes are more sensitive to anions than to cations. Regardless of the cation, the order of contact angles remained consistent across different salt solutions, with polyVBIPS brushes having the highest contact angles, followed by polySVBP and polyDVBAPS brushes. Additionally, monovalent cations induced higher contact angles compared to divalent cations, suggesting stronger binding of divalent cations to sulfonate than monovalent cations.[98]

Ammonium, pyridinium, and imidazolium are known chaotropic cations with low hydration capability, while SO_4^{2-} is a typical kosmotropic anion with a strong hydration ability. Cl^-, Br^-, and NO_3^- anions lie between chaotropes and kosmotropes.[98] The Collins theory suggests that ions with similar hydration capacities form strong ionic bonds. Therefore, Br^- and NO_3^- would have stronger interactions with chaotropic cations, leading to lower contact angles on the polymer brushes. This phenomenon underscores the complex interplay between ions and polymer chains, where strong pairwise ionic interactions promote ionic solvation but weaken their interaction with polymer chains (Figure 10).

The observed influence of metal cations and counterions on the properties of salt-responsive bottlebrush polymers is directly correlated with their responsive behavior. For instance, the varying contact angles of the polymer brushes in different salt solutions reflect changes in their surface hydration and conformational states.[103,104] When exposed to salt solutions with different anions and cations, the brushes exhibit alterations in their hydrophilicity and conformation, affecting their responsiveness. Polymer brushes with higher contact

angles in salt solutions indicate reduced surface hydration and a more collapsed conformation, whereas lower contact angles suggest increased hydration and an elongated conformation. This correlation between contact angles and salt composition illustrates the sensitivity of the bottlebrush polymers to environmental stimuli.[77,78] Moreover, the differences in responsiveness between monovalent and divalent cations further emphasize the intricate interplay between ions and polymer chains. Divalent cations tend to induce stronger interactions with the polymer chains, leading to more pronounced conformational changes compared with monovalent cations.

Understanding the structure−property relationships of salt-responsive bottlebrush polymers concerning metal cations and counterions can be further explored through spherical polyelectrolyte brushes (SPBs). SPBs, consisting of a hydrophobic polymer core and a hydrophilic polyelectrolyte shell, hold significant promise in material and colloid science.[104]

Similar to BBPs, the properties of SPBs are intricately linked to the synthesis conditions and monomer selection. However, while the properties of SPBs in dilute solutions have been extensively studied, the interactions among concentrated SPBs, especially concerning counterions, remain relatively unexplored. Recent investigations focused on understanding how counterions affect interactions among concentrated SPBs, employing advanced characterization techniques such as small-angle X-ray scattering (SAXS), wide-angle X-ray scattering (WAXS), and rheology. These studies revealed intriguing insights into the behavior of SPBs under the influence of counterions.[104]

With increasing SPB concentration, a notable rise in solution viscosity was observed, accompanied by the emergence of "polyelectrolyte peaks" in SAXS curves. These peaks indicated the formation of local ordered structures among polyelectrolyte chains within the SPB dispersions, which corroborates to what we should generally expect of these polymers.[104,105] Moreover, it is evident that counterions played a crucial role in facilitating the formation of these local ordered structures by acting as bridges between polyelectrolyte chains. However, excessive counterions led to the disruption of these structures by shielding electrostatic interactions, resulting in their disappearance.[104] Further analysis revealed that the "structure factor peak" observed in SAXS curves and the "local ordered structure peak" in WAXS curves reflected interactions among concentrated SPBs. Interestingly, these peaks became more pronounced with moderate strengths of counterions, which is also something that we expect (and experimentally proven).[104]

Similar to our observations with spherical polyelectrolyte brushes (SPBs), the addition of counterions to SPB dispersions results in the formation of local ordered structures among the polyelectrolyte chains. This process is also evident in salt-responsive bottlebrush polymers, where conformational changes occur under varying salt concentrations due to the influence of counterions. In concentrated SPB dispersions, the presence of counterions facilitates interactions among polyelectrolyte chains, leading to significant effects on the overall conformation and responsiveness of BBPs.[106]

When counterions are present at moderate concentrations, they promote the formation of local ordered structures within the polymer network. This structural organization can either enhance or inhibit the collapse of BBPs in response to salt, directly affecting their responsive behavior. For example, the specific arrangement of polyelectrolyte chains and the strength

of ionic interactions can determine whether BBPs expand or contract when exposed to different ionic environments.[107] Understanding the influence of metal cations and counterions on the properties of salt-responsive bottlebrush polymers is essential for optimizing their behavior in various applications. By carefully manipulating the salt composition and concentration, researchers can modulate the responsiveness of these polymers and tailor them for specific uses. This ability to control polymer behavior is particularly valuable in fields such as smart surface design and drug delivery systems.

In practical terms, altering the ionic environment surrounding BBPs can lead to precise adjustments in their properties, making them suitable for a wide range of scientific and technological applications. For instance, in drug delivery, the responsive behavior of BBPs can be harnessed to release therapeutic agents at targeted sites within the body, improving the treatment efficacy. Similarly, in the development of smart surfaces, the ability to switch polymer properties in response to environmental changes can lead to innovative materials with tunable characteristics.[108] Overall, the correlation among metal cations, counterions, and polyelectrolyte chains in BBPs underscores the importance of detailed structural and interaction studies. By advancing our understanding of these relationships, we can better design and engineer responsive polymers that meet the demands of diverse applications.

d. Recent Thrusts in Developing Salt-Responsive Bottlebrush Polymers with Antibacterial Properties.
Post-2018, we see a significant development in using salt-responsive bottlebrush polymers with antibacterial properties.[109,110] In general, responsive polymers, capable of altering their composition, structure, or charge characteristics in response to external stimuli, offer an ideal foundation for the development of antibacterial surfaces employing a "killing and release" strategy.[111−113] Typically, these changes induce alterations in surface wettability, influencing the interactions between bacteria and the surface. Leveraging this characteristic, the combination of responsive polymers with bactericides has become a widely explored avenue for achieving an effective antibacterial approach. Considerable progress has been made, with polymers showcasing adaptability to stimuli such as pH, temperature, light, solvent, counterions, and sugar, along with ingeniously designed structures like nanopatterns, hierarchical bilayers, and pendant chain grafting, demonstrating efficient surfaces with "killing and release" antibacterial capabilities.[109] However, several limitations, including disturbances triggering the functional changes, intricate and time-consuming operations, and low release efficiency, have been observed with these surfaces.[114]

In this particular context, the utilization of mixed polymer brushes, composed of different polymers, offers significant advantages in terms of surface property tunability and integration of multiple functions. This is attributed to the ease with which various structural parameters, including component ratio and brush length, can be adjusted in such systems.[109] Taking advantage of these benefits, Yang et al. embarked on fabricating a highly efficient antibacterial surface employing a "killing and release" strategy based on mixed brushes. Two distinct polymer brushes, namely, poly [2-(*tert*-butylamino) ethyl methacrylate] (polyTA) and poly(3-(dimethyl (4-vinylbenzyl) ammonio) propyl sulfonate) (poly-DVBAPS), were chosen as components and prepared through surface-initiated atom transfer radical polymerization (SI-ATRP) and subsequent surface-initiated postmodification

polymerization (SI-PIMP). Through meticulous optimization of the initiator ratio and thickness of each brush, the antibacterial activity of polyTA and the salt-induced bacteria-repellent property of polyDVBAPS were seamlessly integrated into this hybrid system.[109] Antibacterial assays revealed that approximately 93% of attached bacteria were effectively killed during incubation, and subsequently, about 94% of them were released upon treatment with a 1.0 M NaCl solution (Figure 11). Notably, the polyDVBAPS/polyTA mixed brushes
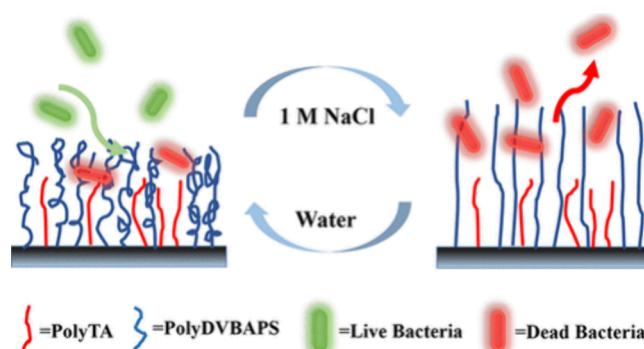

Figure 11. A simple illustration to show the "killing and release" strategy based on mixed brushes developed by Yang et al. Reproduced with permission from ref 109, copyright 2018 American Chemical Society.

exhibited remarkable regeneration capability, retaining both bacterial killing effectiveness and release rate at high levels exceeding 90% even after four "killing and release" cycles. Hence, this salt-responsive mixed polymer coating, with its straightforward structural design yet potent antibacterial properties, holds immense potential across various applications, particularly those requiring long-term reusability.[109]

In the pursuit of achieving antifouling and antibacterial properties, the utilization of electrical potential stands out as a promising method.[115] Numerous studies have highlighted the impact of electrochemical polarization on metal surfaces in influencing bacterial attachment.[116] Reches et al. explored the inhibition of bacterial attachment, bacterial killing, and removal of attached bacteria through the production of hydrogen gas on the cathode during electrochemical reactions.[116] Similarly, the generation of H_2O_2 on the cathode has been employed for killing and releasing attached bacteria.[116] Notably, the anode, as one of the two electrodes in the electrochemical reaction, exhibits lower effectiveness in bacterial resistance and killing, requiring a higher voltage (5 V) than the cathode (3 V) to demonstrate excellent antibacterial properties. During electrochemical reactions, anions and cations move to the anode and cathode, respectively, under the electric field due to the static electric effect, leading to the enrichment of ions on the electrode.[115,116]

Inspired by the ion enrichment on the electrode in an electric field, this study harnessed the electric field to induce salt-responsive properties in a polyzwitterionic brush within a low-concentration salt solution. PolyDVBAPS-grafted indium tin oxides (ITO) were synthesized through surface-initiated atom transfer radical polymerization and utilized as electrodes (Figure 12). When a voltage was applied, chloride ions in the salt solution migrated to the anode, forming a high-concentration ion layer on the electrode surface. This local high concentration of ions induced a conformational change in
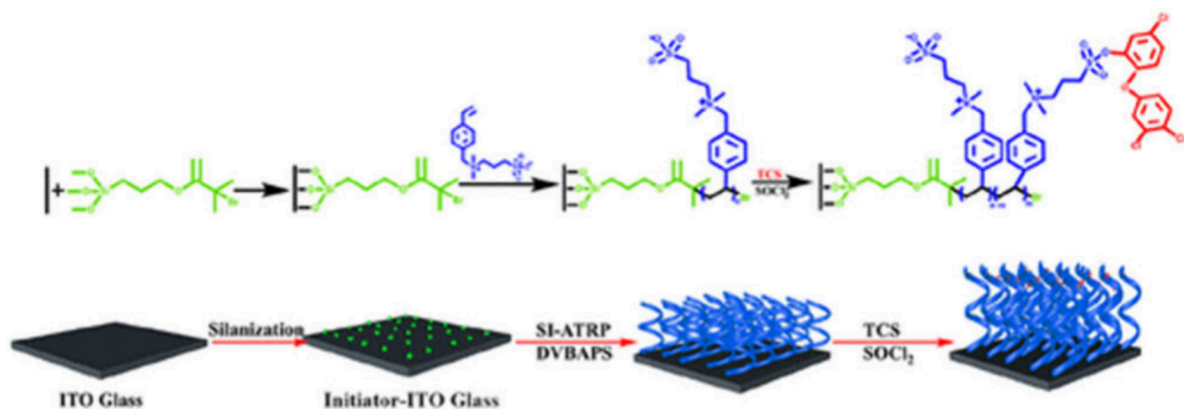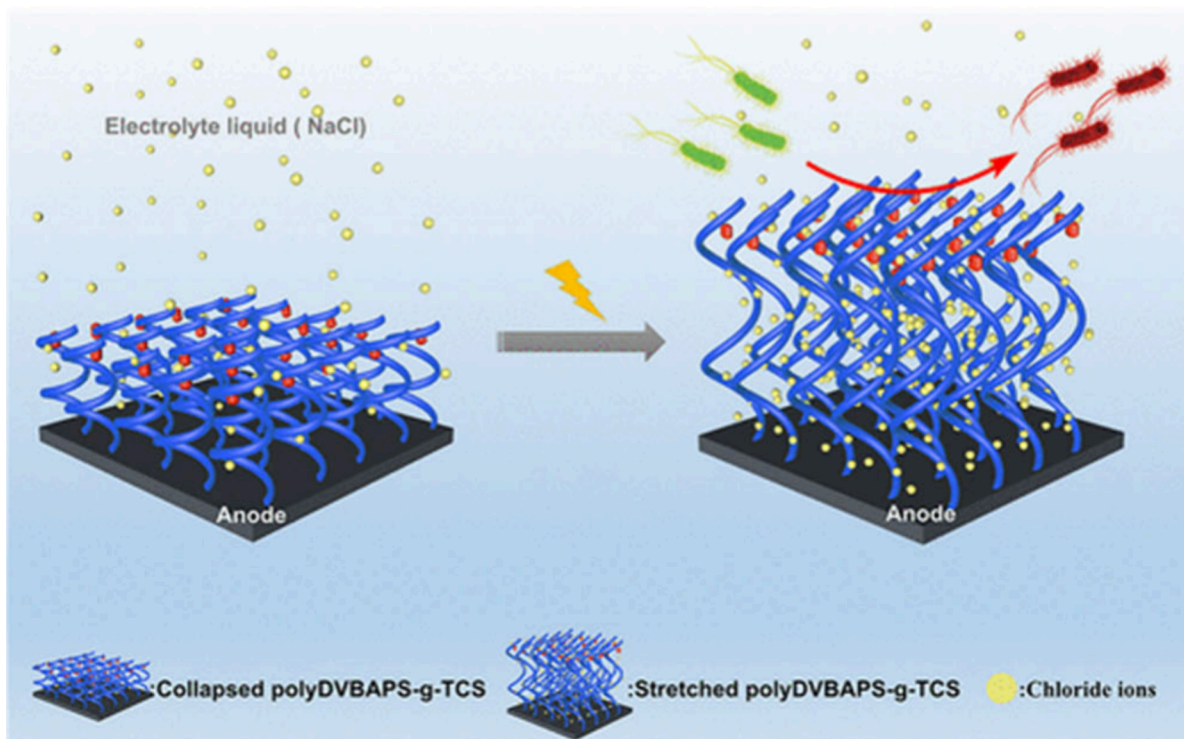
Figure 12. (a) Schematic illustration of the fabrication of polyDVBAPS-*g*-TCS brushes by SI-ATRP processes and subsequent graft of TCS. (b) Schematic representation of the electric-assisted salt-responsive bottlebrush polymer. Reproduced with permission from ref 105, copyright 2019 American Chemical Society.

the brush, leading to the release of the attached bacteria. The study investigated the effects of the salt type, electric field strength, salt solution concentration, and time on bacterial release performance. Additionally, a bactericidal agent, triclosan (TCS), was grafted onto the polyDABAPS brushes.

The presence of TCS exhibited high bactericidal activity and had a minimal impact on the release capabilities of the polyDVBAPS brush. In a 0.12 M NaCl solution with a 3 V/mm electric field, polyDVBAPS-*g*-TCS killed approximately 89% of bacteria and released around 95% of adhered bacteria
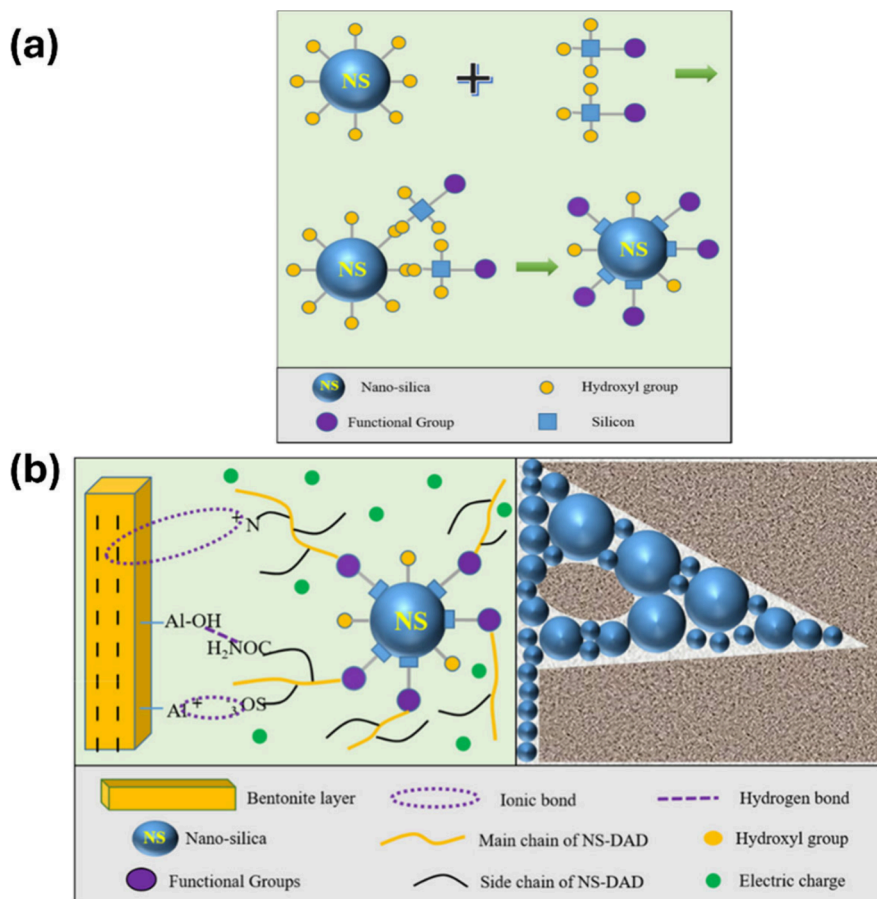
Figure 13. (a) Scheme of silica nanoparticle surface functionalization. (b) Mechanism diagram of interaction between NS-DAD and BT clay. Reproduced with permission from ref 124, copyright 2020 American Chemical Society.

(Figure 12).[105] Therefore, the integration of the electric field significantly reduces the salt concentration required to trigger the salt-responsive behavior of polyzwitterionics, rendering these brushes applicable in biological settings as smart antibacterial surfaces.[105,117]

e. Extending the Salt-Responsive Bottlebrush Polymer's Evolution in Water-Based Drilling Fluids. An emerging application that showcases the potential of zwitterionic polymers is in the realm of water-based drilling fluids.[118] These drilling fluids, essential for oil production from subsurface reservoirs, consist of a complex multiphase dispersion solution comprising bentonite (BT), water, or brine, various treatment agents (inhibitors, filtration reducers), weighting materials (barite and calcium carbonate), and drilling cuttings. One significant challenge faced in the current scenario is the inadequate salt resistance of conventional drilling fluid additives, primarily attributed to the polyelectrolyte effect.[118] This effect entails molecular chains of polymers stretching in water but contracting in brine, compromising their efficacy. Addressing this challenge involves minimizing the polyelectrolyte effect to enhance the salt resistance of polymers in water-based drilling fluids. Traditional additives in drilling fluids, containing strong hydrophilic groups like sulfonic acid groups and carboxylic acid groups, temporarily resist salt intrusion.[119] However, they are fundamentally incompatible with salt, leading to unstable thermodynamic properties in salt-formulated solutions and a subsequent inability to maintain positive performance in high-temperature, high-salinity environments.

In recent years, amphoteric ionic polymers, particularly zwitterionic polymers, have gained attention for their high hydration ability, biocompatibility, and ionic responsiveness. Zwitterionic polymers, characterized by both anions and cations within a single unit or balanced amounts in different monomer units, exhibit unique properties.[120] Notably, they display an "antipolyelectrolyte effect", wherein the polymer chain shrinks in water but gradually extends in saline water, resulting in improved solubility in brine. This distinct behavior arises from the equilibrium state of zwitterions within and between polymer chains, regulating their interaction.[120] The addition of salt ions shields the electrostatic effect on the polymer chain, leading to chain extension.

Research findings, such as those by McCormick, Wang et al., and Yang et al., have delved into the unique characteristics of zwitterionic polymers. McCormick demonstrated the antielectrolytic effect, explaining the unexpected increase in brine. Wang et al. studied the effect of anions on poly-SBMA polymer brushes, revealing opposing changes at low and high ionic strengths. Yang et al. explored the high hydration ability of amphoteric ionic polymers, highlighting the stronger binding ability of poly-SBMA to certain ions.[121−123] These insights contribute to the understanding and potential optimization of zwitterionic polymers for applications in challenging environments such as water-based drilling fluids.

Exploiting the antielectrolyte effect inherent in zwitterionic polymer brushes, a novel approach was employed in the study conducted by Sun et al.[124,125] Silica nanoparticles were modified with vinyl trimethoxysilane (A171), and subse-

quently, a spherical zwitterionic polymer brush, NS-DAD, was synthesized through free radical copolymerization using modified silica nanoparticles. Concurrently, control polymers, including anionic NS-DA, nonionic NS-D, and cationic NS-DD, were also prepared under identical conditions (Figure 13). These four polymers were then evaluated as additives in water-based drilling fluids (WDFs) to assess their performance under challenging reservoir conditions characterized by high temperatures and salinity. NS-DAD, leveraging the antipolyelectrolyte effect, displayed a unique phenomenon where the presence of sodium chloride electrolyte shielded electrostatic interactions within the polyzwitterion molecular chain, inducing a structural transition from a collapsed sphere to a more open helix. On macroscopic terms, NS-DAD exhibited higher viscosity in saturated salt-based mud (SSBM) compared to NS-D, NS-DA, and NS-DD. Microscopic analysis unveiled a distinctive "star-net" structure formed between NS-DAD and the bentonite layer. Energy-dispersive spectroscopy (EDS) analysis of filter cakes demonstrated a significant reduction in chloride and sodium ion content within the bentonite layer induced by NS-DAD (Figure 13).[123,124]

As a result, NS-DAD/SSBM demonstrated superior rheological properties, thermal stability, reduced fluid-loss volume, and a thinner filter cake compared to NS-D/SSBM, NS-DA/SSBM, and NS-DD/SSBM under extreme salinity and high-temperature conditions. The developed fluid-loss additive emerges as a promising solution for effectively mitigating fluid loss in WDFs, particularly in challenging reservoir environments marked by heightened temperatures and salinity. This research not only showcases the practical application of salt-responsive zwitterionic polymers but also offers valuable insights into advancing drilling fluid performance under harsh conditions.[124]

A second strategy carried out by Sun et al. to address the above-discussed problem, where an environmentally friendly and salt-responsive zwitterionic polymer brush, designated as enzymatic lignin nanoparticles (EHL) prepared by intramolecular self-assembly, has been introduced as a fluid-loss additive (EHL-ASN) for WDFs. This innovative approach leverages the antipolyelectrolyte effect of EHL-ASN to address the challenges associated with wellbore instability and collapse, which result from the deterioration of rheological and filtration properties in WDFs due to electrolyte invasion, particularly in high-salinity reservoirs. The study revealed a direct correlation between the ascending viscosity of the EHL-ASN solution and the increasing salinity of the electrolyte, underscoring the evident salt-responsive nature of EHL-ASN. The biological toxicity evaluation demonstrated that the half maximal effective concentration (EC50) of EHL-ASN was 51,900 mg/L, aligning with established direct emission standards (Figure 13).[124]

Furthermore, comprehensive evaluations of rheological and fluid-loss performance in EHL-ASN/WDFs demonstrated substantial improvements in viscosity enhancement and fluid-loss reduction. Notably, EHL-ASN exhibited a remarkable ability to significantly reduce the fluid-loss (FLAPI) of saturated salt-based mud (SSBM) from 194 to 4 mL, marking a decline rate of 97.9%. This not only introduces a novel and environmentally friendly utilization of lignin but also opens avenues for the development of intelligent water-based drilling fluids with enhanced performance.[124]

These findings contribute to the evolving landscape of drilling fluid technology, providing a novel avenue for optimizing the performance in harsh and complex geological settings. The application of salt-responsive zwitterionic polymers represents a strategic approach toward developing more robust and tailored solutions for the oil and gas industry, where reservoir conditions often present formidable challenges. As drilling activities continue to explore unconventional and challenging environments, the insights gained from this research pave the way for enhanced fluid-loss control strategies, ultimately improving the efficiency and effectiveness of drilling operations under extreme conditions.

6. CONCLUSIONS AND FUTURE OUTLOOK

This comprehensive Review seeks to elucidate the evolutionary trajectory of salt-responsive bottlebrush polymers, diverging from the conventional approaches that predominantly rely on stimuli such as temperature, pH, and light. The utilization of salt as a triggering factor imparts a multitude of novel advantages, revolutionizing the landscape of responsive polymer design. In contrast to the more traditional stimuli-responsive strategies, the incorporation of salt responsiveness introduces a paradigm shift in the development of bottlebrush polymers. The distinct advantages associated with this approach underscore its significance in the realm of smart polymer materials. Harnessing salt responsiveness allows for the design of polymers that can dynamically adapt to changes in ionic strength, presenting a versatile platform for a wide range of applications.[126]

The evolutionary trajectory of salt-responsive bottlebrush polymers also brings forth advantages in terms of response kinetics and reversibility.[126] Salt-induced conformational changes in the polymer structure can occur rapidly and exhibit a reversible nature, providing a dynamic and controllable response that aligns with the demands of specific applications.[127] Additionally, the salt-responsive nature of these polymers opens up avenues for exploration in areas such as drug delivery, sensing, and environmental remediation. The adaptability of these polymers to salinity variations positions them as valuable candidates for applications where the responsiveness to changing salt concentrations is a critical factor.

The future outlook for salt-responsive bottlebrush polymers is promising, suggesting a range of potential applications across various industries. One key area of exploration is biomedical applications, where these polymers could play a crucial role in drug delivery systems and tissue engineering. Researchers are expected to focus on enhancing the biocompatibility and specificity of these polymers, making them more effective for targeted drug delivery and controlled release. In the realm of smart surfaces and coatings, the unique responsiveness of these polymers to changes in salt concentrations presents exciting possibilities. Antifouling and antibacterial coatings that can dynamically adjust their properties in response to variations in ionic strength may find applications in medical devices, marine coatings, and other industries where surface performance is critical.[128]

Advancements in salt-responsive polymers hold significant promise for various applications with potential transformative impacts on industries such as oil and gas, water treatment, and drilling fluids. In the oil and gas sector, these polymers offer a unique opportunity to enhance processes, particularly in enhanced oil recovery (EOR). The adaptability of salt-responsive polymers to changing salt concentrations can optimize water-based flooding methods, improving efficiency and performance under diverse reservoir conditions. This

adaptability allows the polymers to dynamically respond to the specific challenges presented by varying salinity levels, contributing to more effective EOR strategies.

The water treatment sector stands to benefit greatly from the utilization of salt-responsive polymers. These intelligent materials, capable of adjusting their conformation in response to salt content variations, hold promise for more efficient water purification and desalination processes. The ability of these polymers to respond to changes in salt concentration can be leveraged to enhance the performance of water treatment technologies, offering a potential solution to the increasing global demand for freshwater resources. In the realm of drilling fluids and industrial processes, salt-responsive bottlebrush polymers have emerged as advanced rheological modifiers. Their distinctive capability to alter the conformation in direct response to salt concentration fluctuations can revolutionize fluid-loss control and stability, particularly in high-salinity conditions. This innovation in rheological control has the potential to address challenges faced during drilling operations in salt-rich environments, ensuring the stability and functionality of drilling fluids.

The integration of environmentally friendly sources, exemplified by enzymatic lignin nanoparticles, into the synthesis of salt-responsive polymers reflects a growing emphasis on sustainability within the field of materials science. As we look toward the future, further research endeavors could extend this commitment to sustainability by exploring alternative, ecofriendly sources for polymer synthesis. By investigating a diverse range of sustainable materials, researchers may uncover novel sources that not only offer salt-responsive properties but also contribute to the overall ecofriendliness of the polymer synthesis process.

Building upon our previous conversation, we aim to advance research in developing a method to deliver stress-regulating agents within plants to alleviate prolonged heat stress. High-aspect-ratio nanomaterials emerge as promising candidates for efficiently transporting these agents into plants.[129]

For example, both tobacco mosaic virus (TMV) and polyethylenimine-functionalized carbon nanotubes have demonstrated effectiveness in delivering genetic material and agents into plants. However, there remains a gap in high-aspect-ratio nanocarriers capable of responding to heat stress and distributing agents to different plant organs.[129,130] Recently, scientists have engineered a temperature-responsive high-aspect-ratio polymer, P[BiBEM-g-(PAA-b-PNIPAm)] (Figure 14), which releases stress-regulating agents within plants when temperatures rise. Loaded with spermidine, these polymer brushes provide protection against heat stress for prolonged periods, effectively managing plant stress for at least 15 days postapplication (Figure 14).[130] These polymers, with diameters around 10 nm and lengths up to 300 nm, showcase the potential of high-aspect-ratio polymer nanocarriers to transport agents into crops in a sustainable and temperature-responsive manner. Longer polymers may accumulate in stems and roots, enhancing the treatment efficacy against vascular and root diseases.

However, these polymer brushes are limited in carrying positively charged agents, restricting their use with negatively charged agents such as DNA and plant hormones. Future designs may explore incorporating weak polycation blocks to broaden their applicability. Furthermore, while current polymers are biocompatible, their poor biodegradability raises sustainability concerns. Future investigations could focus on
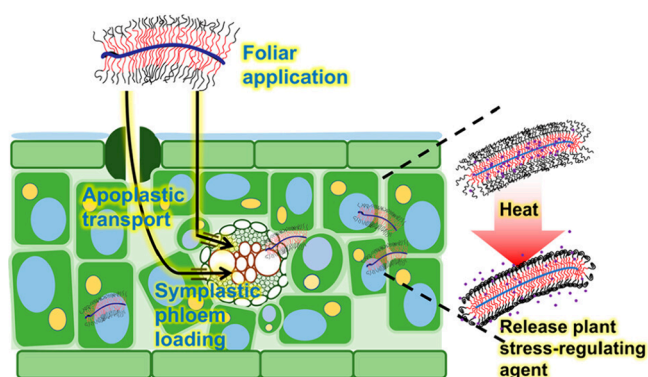

Figure 14. Illustration to visualize temperature-responsive bottlebrush polymers delivering a stress-regulating agent in vivo for prolonged plant heat stress mitigation. Reproduced with permission from ref 130, copyright 2023 American Chemical Society.

developing more sustainable carriers using biodegradable biomaterials.[130]

Overall, the future of salt-responsive bottlebrush polymers is likely to see advancements in diverse applications. Ongoing research efforts are expected to contribute to the development of innovative solutions, making these polymers integral to various industries. As research in this field progresses, this Review aims to shed light on the intricate design principles, synthesis methodologies, and potential applications of salt-responsive bottlebrush polymers. By highlighting the advantages and exploring the unique features brought about by the evolutionary trajectory of salt responsiveness, this Review contributes to the growing body of knowledge in the field of advanced polymer materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c06137.

> Recent examples of stimuli-responsive bottlebrushes, along with their synthetic routes, stimuli, and targeted applications (**Table S1**) and evolution and summary of the salt-responsive bottlebrush polymers along with their synthetic routes, stimulus, and desired targeted application (**Table S2**) (PDF)

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Notes

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